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Synthesis of 5,12-DiHETE Derivative by Palladium-Catalyzed Ternary Coupling between Vinylic Halide, a Vinylic Tin Compound, and Norbornadiene

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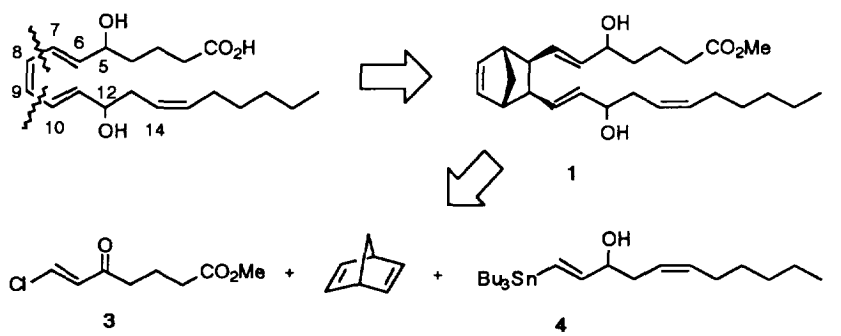
Abstract: A racemic 5,12-DiHETE-8,9-cyclopentadiene Diels-Alder adduct was prepared by palladium-catalyzed ternary coupling between vinylic halide, a vinylic tin compound, and norbonadiene in good yields. Both the halide and tin chain were synthesized in excellent yields by three and four steps, respectively.

Introduction

The palladium-catalyzed ternary coupling reaction between organic halides, organotin compounds, and olefins is an important method for constructing complex molecules, because the tandem two carbon-carbon bonds are formed during a one-pot procedure.[1] Recently we reported that the palladium-catalyzed ternary coupling reaction between organic halides, organotin compounds, and norbornadiene, followed by a retro Diels-Alder reaction produced the cis olefin in good yields.[2] The use of vinylic halide and vinylic tin compounds produces the conjugated triene having a cis structure of the middle ene-moiety. The method appears to have potential use for the synthesis of (5S,6E,8Z,10E,12S,14Z)-5,12-dihydroxy-6,8,10,14-eicosatetraenoic acid [5(S),12(S)-DiHETE] which is the one of the leukotriene families.[3] Our synthetic strategy for using this methodology is as follows:

Scheme 1



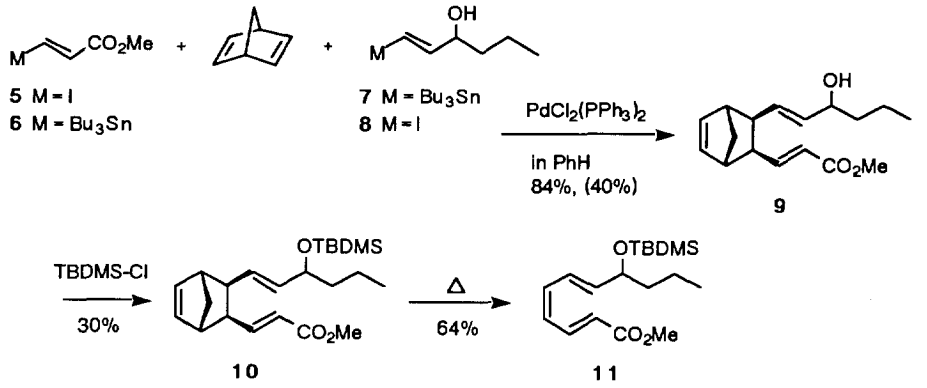
This paper describes the synthesis of a racemic 5,12-DiHETE-8,9-cyclopentadiene Diels-Alder adduct.

Results and Discussion

Preliminary Model Reactions

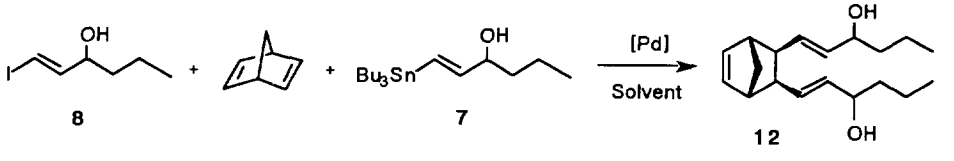
Because stereoselective cross-coupling for palladium-catalyzed reactions of organic halides with organotin compounds is generally accepted,[4] there would be no problems encountered in using (E)-vinylic halides and (E)-vinylic tin compounds. However, the target molecule, has two allylic hydroxyl groups and one carboxylic group. Therefore we investigated the following model reactions shown in Scheme 2.

Scheme 2



The triene **9** was obtained in 84% yield when the combination between (E)-methyl 3-iodoacrylate **5** and 3-hydroxyl-1-hexenyltributyltin **7** was used. On the other hand, the reaction of (E)-3-hydroxyl-1-iodo-1-hexene **8** with (E)-3-tributylstannylacrylate **6** yielded **9** in a low yield (40%). It was found that protection of the hydroxyl group of **9** by tert-butyldimethylsilyl chloride (TBDMS-Cl) followed by the retro Diels-Alder reaction produced **11**, the expected triene in moderate yields, although the procedure for the protection needs to be improved. Instead of the combination of **6** and **8**, the following model reaction was also investigated as shown in Scheme 3.

Scheme 3



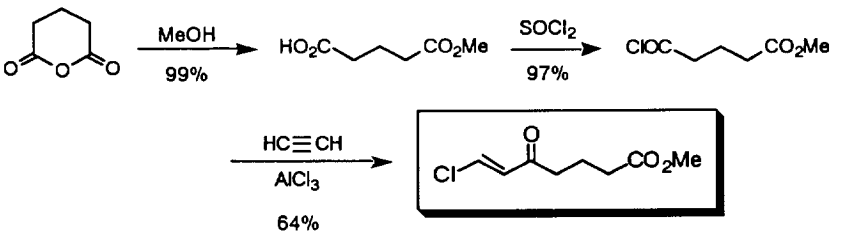
Under the various conditions examined, the yield of 5,6-di(3-hydroxy-1-hexenyl)-2-norbornene **12** was not more than 25%. The presence of the allylic hydroxyl group on the halide was not suitable for this ternary reaction. Thus we have planned to synthesize a racemic 5,12-DiHETE-8,9-cyclopentadiene Diels-Alder adduct in order to obtain the information for the total synthesis of 5(S),12(S)-DiHETE as shown in Scheme 1. The halide and the stannane were selected based on their ease of preparation.

Synthesis of the Halide Chain

Methyl 7-chloro-5-oxo-6(E)-heptenoate **3**, which was found to have sufficient reactivity toward the palladium-catalyzed reaction, was prepared by the following three steps shown in Scheme 4. Methanolysis of glutaric anhydride using a stoichiometric amount of methanol in chloroform as a solvent was carried out under reflux for 5 h to produce glutaric acid monomethylester in nearly quantitative yields. Then it was

treated with thionyl chloride at room temperature for 2 h to yield glutaric acid chloride monomethyl-ester also in good yield. The final step was carried out by bubbling acetylene into the mixture of the acid chloride and 4 equivalents of aluminum chloride in carbon tetrachloride at 0°C for 3 h.[5] The ^{1}H NMR spectra of the methyl 7-chloro-5-oxo-6-heptenoate thus obtained showed two vinylic protons as a doublet (J=14 Hz) indicating the E structure of **3**.

Scheme 4

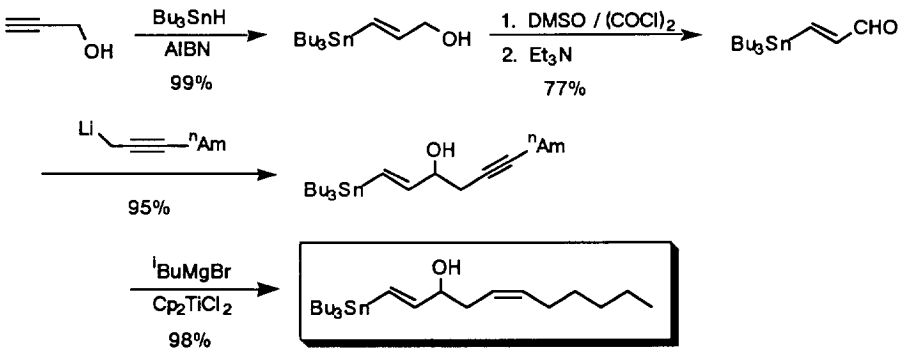


3 δ 7.34, d, J=14Hz
6.53, d, J=14Hz

Synthesis of the Stannane Chain

Synthesis of the stannane chain was carried out by the following four steps shown in Scheme 5.

Scheme 5



4 δ 6.24, d, J=19.2Hz
6.05, dd, J=19.2, 5Hz
5.57, dt, J=10.6, 7.1Hz
5.38, dt, J=10.6, 7.1Hz

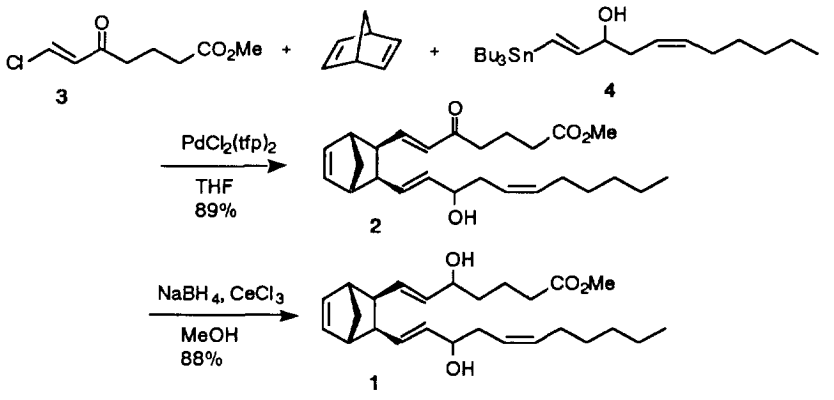
Hydrostannylation of propargyl alcohol,[6] followed by Swern oxidation produced β-stannylacryl aldehyde. Its ^{1}H NMR spectra showed two vinylic protons at 7.81(d, J=19.2Hz) and 6.63(dd, J=19.2, 7.6Hz) which indicates the E structure. The reaction of this with 1-lithio-2-octyne, followed by hydromagnesation[7] produced the expected stannane chain in good yields. The ^{1}H NMR spectra of **4** was consistent with the expected structure.

Synthesis of 5,12-DiHETE-8,9-cyclopentadiene Diels-Alder Adduct by Palladium-catalyzed Ternary Coupling

The palladium-catalyzed ternary coupling reaction was carried out by using **3** and **4** in the presence of dichlorobis[tri(2-furyl)phosphine]palladium, $PdCl_2(tfp)_2$,[8] to produce the expected **2** in good yields.

Reduction of the 5-carbonyl group was also attained in excellent yields using sodium tetrahydroborate in the presence of cerium chloride.[9]

Scheme 6



In summary, it was found that the 5,12-DiHETE-8,9-cyclopentadiene Diels-Alder adduct 1 could be prepared by relatively short steps via the palladium-catalyzed ternary coupling reaction between the vinylic halide, the vinylic tin compound, and norbornadiene in good yields. These results provide useful route for the total synthesis of 5(S),12(S)-DiHETE; remaining problems include the introduction of the two allylic stereogenic centers and efficient protection of the hydroxyl groups.

Experimental Section

The ^{1}H-NMR spectra were recorded on either a Varian Gemini 200 (200MHz) or a JEOL JMN-α500 (500MHz) instrument. The chemical shifts are reported in ppm (δ) downfield from tetramethylsilane (δ=0ppm) or residual chloroform (δ=7.26ppm). The signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet; br s, broad singlet. The coupling constants (J) are given in hertz. The ^{13}C-NMR spectra were recorded on either a Varian Gemini 200 (50MHz) or a JEOL JNM-α500 (125MHz) instrument. The chemical shifts are reported in ppm (δ) downfield from tetramethylsilane (δ=0ppm) or residual chloroform (δ=76.9ppm). IR spectra were recorded on a JASCO A-100 spectrophotometer and are reported in wave numbers (cm^{-1}). GC-MS spectra were measured on Shimadzu QP2000A instrument and are reported in order of the molecular ion peak and the four highest peaks (intensity). GC analyses were performed on a GC-8A instrument using a 2m column packed with 5% SE-30 on Celite 545. LC analyses were carried out using a LC-08 instrument from Japan Analytical Industry Co.Ltd. Analytical TLC was performed on 0.2mm pre-coated silica gel plates purchased from E. Merck. The products were purified using the flash chromatography technique on Kieselgel 60 (70-200 mesh ASTM, 0.063-0.200mm) purchased from E. Merck. Unfortunately, complete elimination of the solvent used in chromatography could not be attained. Thus the data from this elemental analyses include the solvent. Elemental analyses were carried out at the Analytical Laboratory of Gunma University.

Commercial grade reagents and solvents were used as supplied with the following exceptions; Diethyl ether and tetrahydrofuran (THF) were freshly distilled from sodium benzophenone ketyl. Dichloromethane

was freshly distilled from calcium hydride. Hexamethylphosphoric triamide (HMPA), N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), and N-methyl-2-pyrrolidone (NMP) were distilled from calcium hydride and stored over 4A molecular sieves. Benzene was distilled from sodium wire and stored over sodium wire. Methanol was distilled from magnesium methoxide and stored over 4A molecular sieves. Ethanol was distilled from sodium ethoxide and stored over 4A molecular sieves. Tributyltin hydride[10] and palladium catalysts[11] were prepared by the methods described in the literatures. All reactions sensitive to oxygen or moisture were carried out under an argon atmosphere.

(E)-Methyl 3-tributylstannylacrylate (6). A mixture of tributyltin hydride (5.8g, 20mmol), methyl propiolate (2.1g, 25mmol) and α,α'-azobis(isobutyronitrile) (catalytic amount) in benzene (200mL) was refluxed overnight. After concentration of the reaction mixture, the product was purified by column chromatography(silica gel, benzene) (3.0g, 40%); ^{1}H-NMR (200MHz) δ 7.75 (d, J=19Hz, 1H with Sn coupling of 16, 38Hz), 6.31 (d, J=19Hz, 1H with Sn coupling of 16, 38Hz), 3.76 (s, 3H), 1.60-1.24 (m, 18H), 0.90 (t, J=7Hz, 9H); IR (NaCl) 1720, 1568, 990 cm^{-1}.

(E)-Methyl 3-iodoacrylate (5). Iodine (0.4g, 1.7mmol) was added to the solution of **6** (0.6g, 1.6mmol) in dichloromethane (15mL) at 0°C. The mixture was stirred for 2 h at room temperature. After the solvent was removed in vacuo, the product was purified by Kugelrohr distillation (0.15g, 46%); b.p. 130°C/760mmHg; m.p. 37-38°C; ^{1}H-NMR (200MHz) δ 7.90 (d, J=14Hz, 1H), 6.89 (d, J=14Hz, 1H), 3.75 (s, 3H).

1-Tributylstannyl-1-hexen-3-ol (7). Prepared by the reaction of tributyltin hydride (8.78g, 30mmol) with 1-hexyn-3-ol (3.0g, 30mmol) in the presence of α,α'-azobis(isobutyronitrile) (catalytic amount) in benzene (200mL). The product was isolated by column chromatography (silica gel, hexane) (7.35g, 63%); ^{1}H-NMR (200MHz) δ 6.19-5.92 (m, 2H), 4.14-4.02 (m, 1H), 3.74 (br d, J=6Hz, 1H), 1.60-1.24 (m, 22H), 0.90 (t, J=7Hz, 12H); IR (NaCl) 3325,1568, 990 cm^{-1}.

1-Iodo-1-hexen-3-ol (8). Prepared by the reaction of **7** (1.9g, 5mmol) with iodine (1.3g, 5mmol). The product was isolated by column chromatography (silica gel, chloroform) (0.85g, 75%); ^{1}H-NMR (200MHz) δ 6.59 (dd, J=14.5, 6Hz, 1H), 6.34 (dd, J=14.5, 1Hz, 1H), 4.16-4.05 (m, 1H), 1.72 (br s, 1H), 1.60-1.24 (m, 4H), 0.93 (t, J=7Hz, 3H); IR (NaCl) 3340, 1600 cm^{-1}; GC-MS M$^+$ m/e 228(7), 55(100), 43(66), 73(63), 57(42).

General Procedure for Model Reactions: A tube containing a mixture of norbornadiene (2mmol), vinylic halide (1mmol), the vinylic tin compound (1mmol) and the palladium complex (0.01mmol) in solvent(1mL) was sealed in vacuo. The reaction was carried out in a thermobath for a fixed period of time at 80°C. After the reaction mixture was washed with aqueous potassium fluoride, the product was isolated by flash column chromatography.

Methyl 3-[6-(3-hydroxy-1-hexen-1-yl)-2-norbornen-5-yl]acrylate (9). ^{1}H-NMR (200MHz) δ 6.93-6.72 (m, 1H), 6.19 (br s, 2H), 5.85-5.68 (m, 1H), 5.48-5.20 (m, 2H), 4.08-3.96 (m, 1H), 3.72(s, 3H), 2.73 (br s, 2H), 2.61 (br d, J=9Hz, 2H), 2.40 (br d, J=9Hz, 1H), 2.33 br s, 1H), 1.70 (br d, J=8Hz, 1H), 1.47-1.23 (m, 4H), 0.92 (t, J=7Hz, 3H); IR (NaCl) 3400, 1720, 1640, 1430, 900 cm^{-1}.

5,6-Bis(3-hydroxy-1-hexen-1-yl)-2-norbornene (12). ^{1}H-NMR (200MHz) δ 6.10-5.95 (m, 6H), 4.23-4.15 (m, 2H), 2.67-2.36 (m, 7H), 1.80-1.22 (m, 9H), 0.94 (t, J=7Hz, 6H); IR (NaCl) 3420, 1630 cm^{-1}.

Methyl 3-[6-(3-tert-butyldimethylsilyloxy-1-hexen-1-yl)-2-norbornen-5-yl]acrylate (10). A mixture of 9 (0.21g, 0.75mmol), TBDMS-Cl (0.20g, 1.3mmol), and imidazole (0.13g, 2mmol) in DMF (1.5mL) was stirred for 20 h at room temperature. The reaction mixture was hydrolyzed with saturated aqueous sodium bicarbonate, and then the organic layer was extracted with hexane. The product was isolated by column chromatography (silica gel, chloroform) (0.09g, 30%); ^{1}H-NMR (200MHz) δ 6.92-6.74 (m, 1H), 6.27-6.13 (m, 2H), 5.78 (dd, J=15.5, 3.4Hz, 1H), 5.43-5.32 (m, 2H), 4.06-3.97 (m, 1H), 3.72 (s, 3H), 2.70 (br d, J=9Hz, 2H), 2.33 (br d, J=9Hz, 2H), 1.74-1.16 (m, 6H), 0.95-0.83 (m, 12H), 0.05 (s, 6H); GC-MS M^+ m/e 333 (M^+-t-Bu 47), 73(100), 89(61), 41(35), 55(26).

Methyl 8-tert-butyldimethylsilyloxy-2,4,6-undecatrienoate (11). A retro Diels-Alder reaction was performed by heating **10** (0.049g, 0.13mmol) for 2 h at 185°C using a Kugelrohr apparatus. (0.026g, 64%); ^{1}H-NMR (200MHz) δ 6.37-6.03 (m, 4H), 5.86 (d, J=15.9Hz, 2H), 4.27-4.18 (m, 1H), 3.68 (s, 3H), 1.60-1.24 (m, 4H), 0.95-0.85 (m, 12H), 0.05 (t, J=6Hz, 6H); GC-MS M^+ m/e 267(M^+-t-Bu 2.8), 73(100), 107(67), 89(63), 241(39).

Methyl glutarylchloride. Mono-methyl glutarate was prepared by heating a mixture of glutaric anhydride (25g, 0.22mol) and absolute methanol (7g, 0.22mol) in chloroform (200mL) under reflux for 5 h. Evaporation of the solvent afforded monomethyl glutarate (32g, 0.22mol), which was used without further purification and treated with thionyl chloride (52g, 0.44mol) over a period of 3 h. The product was isolated by distillation (35g, 97%); b.p. 67°C/2.5mmHg; ^{1}H-NMR (200MH z) δ 3.70 (s, 3H), 3.01 (t, J=7Hz, 2H), 2.42 (t, J=7Hz, 2H), 2.02 (p, J=7Hz, 2H); IR (NaCl) 1790, 1730 cm^{-1}.

(E)-Methyl 7-chloro-5-oxo-6-heptenoate (3). Anhydrous aluminum chloride (53g, 0.4mol) was suspended in carbon tetrachloride (70mL) in a 300mL three-necked flask fitted with a glass gas-inlet tube connected to an acetylene source and an addition funnel containing methyl glutarylchloride (16.5g, 0.1mol) dissolved in carbon tetrachloride (20mL). The flask was cooled in an ice bath while the acid chloride solution was added to the acetylene-saturated aluminum chloride suspension. The acetylene stream was continued for 3 h while the mixture was allowed to warm to ambient temperature. The black reaction mixture was poured into an ice-salt mixture and the organic layer was extracted with ether. The dark ether extracts were washed with water and brine and dried over sodium sulfate. The product was isolated by flash column chromatography (silica gel, dichloromethane) (12.1g, 64%); ^{1}H-NMR (200MHz) δ 7.34 (d, J=14Hz, 1H), 6.53 (d, J=14Hz, 1H), 3.68 (s, 3H), 2.62 (t, J=7Hz, 2H), 2.38 (t, J=7Hz, 2H), 1.95 (p, J=7Hz, 2H); ^{13}C-NMR (50MHz) δ 196.5, 173.5, 136.7, 132.2, 51.3, 39.6, 32.4, 18.4; IR (NaCl) 1725, 1685, 1580 cm^{-1}; GC-MS M^+ m/e 191(0.1), 89(100), 91(34), 56(17), 60(17); Anal. Calcd. for $C_8H_{11}O_3Cl$·0.35CH_2Cl_2: C, 45.51; H, 5.35. Found: C, 45.25; H, 5.46.

3-Tributylstannyl-2-propen-1-ol. The reaction of tributyltin hydride (21.6g, 74mmol) with propargyl alcohol (4.5g, 80mmol) in the presence of a,a'-azobis(isobutyronitrile) (catalytic amount) in hexane (200mL) was carried out. The product was isolated by column chromatography (silica gel, chloroform) (25.6g, 99%); ^{1}H-NMR (200MHz) δ 6.87-6.08 (m, 2H), 4.24-4.08 (m, 2H), 3.48 (s, 1H), 1.55-1.24 (m, 18H), 0.90 (t, J=7Hz, 9H); ^{13}C-NMR (50MHz) δ 147.2, 128.3, 66.2, 28.8, 27.0, 13.4, 9.1; IR (NaCl) 3300, 1600 cm^{-1}; Anal. Calcd. for $C_{15}H_{32}OSn$+0.4$CHCl_3$: C, 46.84; H, 8.27. Found: C, 47.08; H, 8.18.

(E)-3-Tributylstannylacrolein. A solution of DMSO (0.38g, 4.8mmol) in dichloromethane (5mL) was added dropwise to oxalyl chloride (0.2mL, 2.4mmol) in dichloromethane (20mL) at -78∞C. After the solution was stirred for 2 min, 3-tributylstannyl-2-propen-1-ol (0.69g, 2mmol) was rapidly added. After

stirring for 15 min, triethylamine (0.8g, 8mmol) was added dropwise and stirred for 5 min. The temperature of the mixture was then allowed to rise to room temperature. The mixture was hydrolyzed with water and then extracted with dichloromethane. The combined organic layer was washed with brine and dried over sodium sulfate. The product was isolated by flash column chromatography (slica gel, chloroform) (0.53g, 77%); ^{1}H-NMR (200MHz) δ 9.42 (d, J=7.6Hz, 1H), 7.81 (d, J=19.2Hz, 1H), 6.63 (dd, J=19.2, 7.6Hz, 1H), 1.55-1.24 (m, 18H), 0.90 (t, J=7Hz, 9H); ^{13}C-NMR(50MHz) δ 193.9, 163.4, 147.7, 28.7, 26.9, 13.3, 9.5; IR (NaCl) 2700, 1680 cm^{-1}; GC-MS M^+ m/e 289(M^+-Bu 65), 233(100), 177(92), 43(45), 121(42); Anal. Calcd. for $C_{15}H_{30}OSn$+0.15$CHCl_3$: C, 50.13; H, 8.37. Found: C, 50.04; H, 8.48.

(E)-1-Tributylstannyl-1-undecen-5-yn-3-ol. To a stirred solution of (E)-3-tributylstannyl-acrolein (2.7g, 7.7mmol) in THF (20mL) was added dropwise 1-lithio-2-octyne, which was prepared by the reaction of 2-octyne (1.5 mL, 10 mmol) and tert-butyllithium (1.6M in pentane, 5 mL, 8 mmol), at -78°C. The temperature of the mixture was allowed to rise to room temperature. After 1 h of additional stirring, the mixture was hydrolyzed with aqueous ammonium chloride and the organic layer was then extracted with ether. The product was isolated by flash column chromatography (silica gel, chloroform) (3.3g, 95%); ^{1}H-NMR (200MHz) δ 6.24 (d, J=19.2Hz, 1H), 6.05 (dd, J=19.2, 5Hz, 1H), 4.25-4.12 (m, 1H), 2.48-2.38 (m, 2H), 2.22-2.12 (m, 2H), 2.08 (d, J=9Hz, 1H), 1.55-1.24 (m, 24H), 0.90 (t, J=7Hz, 9H), 0.88 (t, J=7Hz, 3H); ^{13}C-NMR (50MHz) δ 149.2, 128.6, 79.0, 75.2, 73.1, 30.8, 28.7, 28.5, 27.0, 22.1, 21.9, 18.4, 13.6, 13.3, 9.5; GC-MS M^+ m/e 399(M^+-Bu 100), 177(96), 43(89), 137(67), 233(60).

1-Tributylstannyl-1E,5Z-undecadien-3-ol (4). To an ice-cooled solution of isobutylmagnesium bromide (1.7M/ether, 10mL, 17mmol) was added titanocene dichloride (0.085g, 0.34mmol). The solution was stirred for 30 min at 0∞C, and (E)-1-tributylstannyl-1-undecen-5-yn-3-ol (2.6g, 5.7mmol) was added. Stirring was continued for 12 h at room temperature, and then the solution was slowly poured into a mixture of ice and aqueous ammonium chloride with vigorous stirring. The organic layer was separated, dried over sodium sulfate, and concentrated in vacuo. The product was purified by flash column chromatography (silica gel, dichloromethane) (2.57g, 98%); ^{1}H-NMR (200MHz) δ 6.24 (d, J=19.2Hz, 1H), 6.05 (dd, J=19.2, 5Hz, 1H), 5.57 (dt, J=10.6, 7.1Hz, 1H), 5.38 (dt, J=10.6, 7.1Hz, 1H), 4.25-4.12 (m, 1H), 2.35-2.28 (m, 2H), 2.15-1.90 (m, 3H), 1.65-1.24 (m, 24H), 0.89 (t, J=7Hz, 12H); ^{13}C-NMR (50MHz) δ 150.3, 133.4, 127.8, 124.5, 74.6, 34.9, 31.3, 29.1, 28.8, 27.2, 27.0, 22.3, 13.7, 13.4, 9.1; Anal. Calcd. for $C_{23}H_{46}OSn$+0.2CH_2Cl_2: C, 58.75; H, 9.86. Found: C, 58.83; H, 9.64.

Methyl 7-[6-(3-hydroxy-1,5-undecadien-1-yl)-2-norbornen-5-yl]-5-oxo-6-heptenoate (2). A tube containing a mixture of norbornadiene (0.36g, 4mmol), **3** (0.38g, 2mmol), **4** (0.914g, 2mmol) and $PdCl_2(tfp)_2$ (0.013g, 0.02mmol) in THF (1mL) and the solvent was sealed in vacuo. The reaction was carried out in a thermobath for 24 h at 80°C. The reaction mixture was washed with aqueous potassium fluoride, and then subjected to flash column chromatography (silica gel, chloroform/ether = 9) to isolate the product (0.71g, 88%); ^{1}H-NMR (500MHz) δ 6.77-6.70 (m, 1H), 6.24-6.18 (m, 2H), 6.04 (dd, J=15.5, 6.7Hz, 1H), 5.56-5.30 (m, 4H), 4.15-4.06 (m, 1H), 3.67 (s, 3H), 2.78-2.71 (m, 2H), 2.66-2.52 (m, 2H), 2.38-2.12 (m, 7H), 2.06-2.01 (m, 2H), 1.96-1.90 (m, 2H), 1.72 (dd, J=14, 9Hz, 1H), 1.45 (dd, J=8, 1.2Hz, 1H), 1.36-1.24 (m, 6H), 0.88 (t, J=6.6Hz, 3H); ^{13}C-NMR (125MHz) δ 199.9 and 199.8, 174.1, 150.9, 138.1 and 138.0, 137.1, 134.0 and 133.8, 133.2, 132.5, 129.9 and 129.8, 124.5, 71.9, 51.5, 48.0 and 47.8, 47.4 and 47.1, 46.0 and 45.9, 45.8 and 45.7, 42.9, 38.5, 35.2 and 35.1, 32.8, 31.2, 29.0, 27.2, 22.3, 19.4, 13.8; IR (NaCl) 3450, 1730, 1660, 1610 cm^{-1}. Anal. Calcd. for

$C_{26}H_{38}O_4$+0.15$CHCl_3$: C, 72.62; H, 8.89. Found: C, 72.70; H, 8.84. The ^{13}C NMR spectra showed that the product was the mixture of diastereomers.

Methyl 7-[6-(3-hydroxy-1,5-undecadien-1-yl)-2-norbornen-5-yl]-5-hydroxy-6-heptenoate (1). To a solution of **2** (5.62g, 1.35mmol) in methanol (10mL) was added cerium(III) chloride heptahydrate (0.51g, 1.35mmol) and sodium tetrahydroborate (0.051g, 1.35mmol) was then slowly added. After stirring for 1 h, the reaction was quenched with 1N-hydrochloric acid. After the methanol was removed in vacuo, the organic layer was extracted with dichloromethane and dried. The product was isolated by flash column chromatography (silica gel, chloroform followed by ether) (0.50g, 88%); ^1H-NMR (500MHz) δ 6.19-6.12 (m, 2H), 5.56-5.32 (m, 6H), 4.14-4.02 (m, 2H), 3.67 (s, 3H), 2.67-2.63 (m, 2H), 2.40-2.20 (m, 6H), 2.08-1.97 (m, 2H), 1.74-1.43 (m, 4H), 1.41-1.21 (m, 10H), 0.89 (t, J=6.4Hz, 3H); IR (NaCl) 3400, 1730, 1570 cm^{-1}. Anal. Calcd. for $C_{26}H_{40}O_4$+0.25$CHCl_3$: C, 70.62; H, 9.09. Found: C, 70.78; H, 9.30.

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